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REVIEW PAPER

Glioma Pericytes Promote Angiogenesis by Producing Periostin

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Abstract
Glioma is the prevalent aggressive primary brain tumor, with a very poor prognosis. The absence of advanced understanding of the roles played by the cells within the glioma microenvironment limits the development of effective drugs. A recent study indicates that periostin expressed by pericytes is crucial for glioma angiogenesis. Here, we describe succinctly the results and implications of this discovery in what we know about pericytes within the glioma microenvironment. The emerging knowledge from this work will benefit the development of therapies for gliomas.

Keywords Pericytes · Glioma · Tumor microenvironment · Periostin

Introduction

In the past few decades, oncology research groups have focused their concentration mostly on malignant cells (Manini et al. 2018). Nevertheless, emerging evidence demonstrates that the surroundings where these malignant cells are located play key roles in tumor development (Vannucci 2015). These surroundings are defined as tumor microenvironment, which contains signaling molecules, growth factors, extracellular matrix, and non-malignant cells, such as immune cells, mesenchymal stem cells, endothelial cells, neurons, fibroblasts, adipocytes, pericytes, and others (Picoli et al. 2020; De Vleeschouwer and Bergers 2017; Prazeres et al. 2020; Azevedo et al. 2017, 2018a; Paiva et al. 2017, 2018; Lousado et al. 2017; de Alvarenga et al. 2018). The constituents of the tumor microenvironment by communicating with cancer cells, as well as between themselves, influence tumor initiation, progress, invasion, and metastasis (Quail and Joyce 2013).

Gliomas are the most common presentations of primary brain tumors. Their classification is based on histopathological and clinical characteristics established by the World Health Organization (WHO), and are typified by high mortality due to their aggressiveness (Ostrom et al. 2014). Although meaningful increment has been made in our knowledge of disease pathogenesis, improving diagnostics, gliomas prognosis is still very poor (Weller et al. 2015). The initiation and progression of gliomas are attributed to genetic mutations in single cells. Despite several improvements, unfortunately, treatments like surgery, radiotherapy, and chemotherapy can rarely control completely this disease (Birbrair et al. 2017b; Roberts and Munson 2020). Patients with glioma have a limited long-term survival, mainly due to the escape of tumor initiating cells of the initial treatments (Krex et al. 2007). Since these escaped cells are more resistant to treatments, adjuvant therapies that could effectively destroy these remaining cancer cells would have a considerable impact on anti-glioma therapy. The absence of an accurate comprehension of the cellular and molecular processes that mediate glioma advancement impede the development of efficient anti-glioma therapies.

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Interestingly, cerebral microvessels have higher pericytes/endothelial cells ratio (10–30 fold) than other tissues (Winkler et al. 2014), therefore, contribution of blood vessels, specifically pericytes, to the establishment of glioma microenvironment have attracted interest in the recent years. Pericytes were defined, more than a century ago, as a population of contractile cells with long projections encircling the blood vessel walls (Rouget 1873; Zimmermann 1923; Birbrair et al. 2015). The narrow microscopic competence, earlier than the twenty-first centurys culminated in the concept of pericytes being merely static perivascular supporting cells. Lately, numerous modern tools, including confocal microscopes and transgenic mouse models, influenced positively the extending knowledge on recently discovered novel functions of pericytes in pathophysiology (Birbrair et al. 2015).

Pericytes play important roles in tumoral angiogenesis (Birbrair et al. 2014c). Nevertheless, the molecular mechanisms that govern pericytes behavior within the glioma microenvironment remain unknown. In a recent article in *Journal of Neuropathology & Experimental Neurology*, Huizer and colleagues suggest that periostin expressed by pericytes is essential for angiogenesis within the glioma microenvironment (Huizer et al. 2020). The authors analyzed periostin expression in human gliomas, and found that its expression in high-grade glial tumors was increased when compared with normal brain tissue. This expression was localized in cells associated with brain blood vessels, more specifically in PDGFRβ + pericytes. Importantly, periostin expression was not detected in glial cells in vivo (Huizer et al. 2020). To understand the role of periostin in pericytes, Huizer and colleagues performed serial in vitro experiments using human cell lines of pericytes, astrocytes, endothelial cells and U87 glioma cells. These experiments revealed that Glioma-derived factors in vitro enhance periostin expression in pericytes. Interestingly, silencing of periostin expression in pericytes resulted in a decrease of their angiogenic capacity in vitro, indicating that periostin is necessary for pericytes-dependent angiogenesis in glioma pathogenesis. This study provides a new possible role of periostin in pericytes during normal blood vessel formation, once this protein was also highly expressed in arteriovenous malformations samples. Here, we critically analyze the discoveries from this study, evaluating recent progress in our knowledge on the glioma microenvironment and pericytes biology (Fig. 1).

Perspectives/Future Directions

The outcome from this study claiming the pro-angiogenic role of periostin in pericytes in the glioma microenvironment are based on experiments carried out using pericytes grown in vitro. Remarkably, cell cultures are characterized by artificial conditions and high concentration of mitogens. Therefore, they can induce specific features in pericytes which may not be found in the corresponding endogenous glioma pericytes in vivo (Snippert and Clevers 2011; Birbrair et al. 2017a). Transgenic mice are presently the most trustworthy approach to examine the function of specific cell populations in vivo (Buckingham and Meilhac 2011). These mice have been extensively utilized to evaluate different components

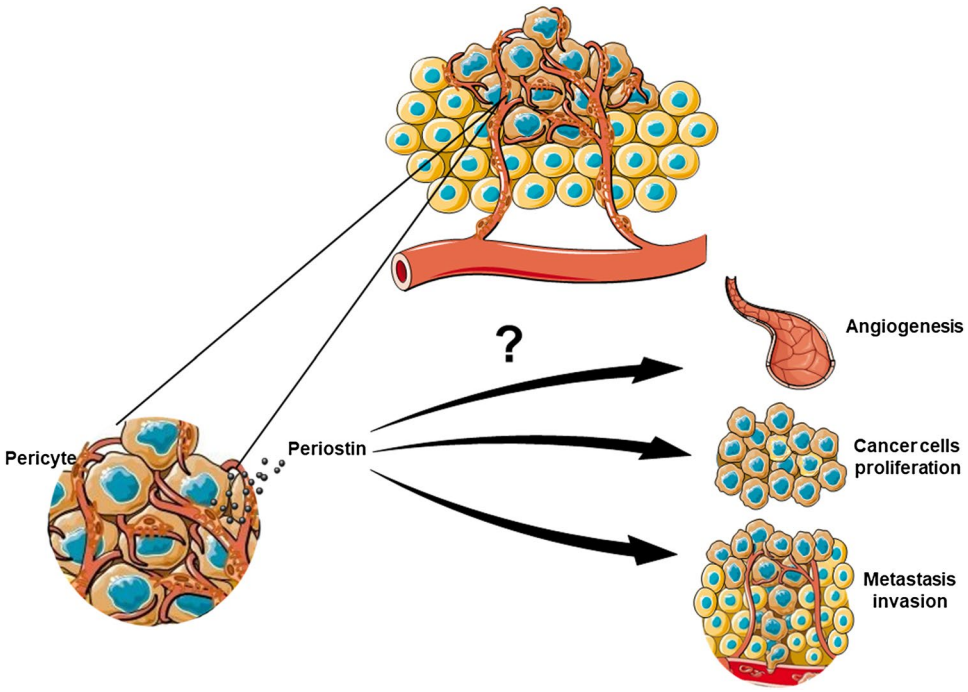

Fig. 1 Schematic illustrating possible roles of periostin derived from pericytes in the glioma microenvironment. Pericytes are attached to the brain vasculature. The study of Huizer and colleagues now indicates that periostin expressed by pericytes can induce angiogenesis within the brain tumor (Huizer et al. 2020). Other studies show the importance of periostin for cancer cells proliferation and migration to secondary sites. State-of-art modern technologies will reveal in detail whether periostin derived from pericytes is essential for these processes within the glioma microenvironment

within various tissue microenvironments (Silva et al. 2018a, b; Borges et al. 2017; Andreotti et al. 2018a, b, 2019; Henriques et al. 2018; Guerra et al. 2018a; Leonel et al. 2019; Magno et al. 2019; Kanashiro et al. 2020; Miranda et al. 2020; Goncalves et al. 2019). The possibility to eliminate one gene in pre-defined cells within adult mouse models has answered multiple questions relative to the molecular mechanisms that govern numerous physiologic and pathologic processes. In the cerebral tumor microenvironment, the key players that control disease progression remain poorly defined (Andreotti et al. 2017; Birbrair 2017).

A study using murine orthotopic glioblastoma xenograft mouse model identified periostin being produced by glioma stem cells (Zhou et al. 2015; Guerra et al. 2018b). Interestingly, lineage tracing shows that, in the glioma microenvironment, cancer stem cells originate pericytes that support blood vessel function and tumor development (Zhou et al. 2017; Cheng et al. 2013). These findings support the possibility that periostin may be important also in vivo in the glioma microenvironment. Huizer et al. (2020) now proposed that periostin in pericytes is essential for glioma angiogenesis. Nonetheless, periostin has not been conditionally eliminated from cerebral pericytes in vivo, therefore there is no direct proof that pericytes are the only/main cells secreting periostin and inducing angiogenesis during glioblastoma progression. This issue may be examined, thanks to recent technological breakthroughs, which allow us to specifically genetically eliminate periostin from brain pericytes during glioma development. The main findings from this study are based on the data in which periostin expression was silenced with siRNA in vitro. It would be interesting in future studies to explore the role of periostin in vivo as well. To perform pericyte-specific periostin targeting in vivo, a specific mouse model can be used in future studies, i.e., PDGFRβ-CreERT2/periostin floxed mice (Gerl et al. 2015). This model would allow genetic elimination of periostin in different stages of glioma progression and define the role of periostin on perivascular PDGFRβ-expressing cells during glioma development.

Pericytes are heterogeneous in their distribution, origin, phenotype and function (Sims 2000, 1991; Armulik et al. 2011; Dias Moura Prazeres et al. 2017; Birbrair and Delbono 2015; Coatti et al. 2017; Prazeres et al. 2018a, b; Picoli et al. 2019; Valle et al. 2020; Isasi and Olivera-Bravo 2020), and several subpopulations have been characterized in various tissues (Asada et al. 2017; Khan et al. 2016; Birbrair et al. 2013c, d; Göritz et al. 2011; Stark et al. 2013; Birbrair and Frenette 2016; Costa et al. 2018; Santos et al. 2018; Almeida et al. 2018), including the brain (Göritz et al. 2011; Birbrair et al. 2014a; Azevedo et al. 2018b; Santos et al. 2019). In the central nervous system, we identified two pericyte subtypes, based on Nestin-GFP expression (Birbrair et al. 2011, 2013b), type-1 (NG2 + /Nestin-GFP-) and type-2 (NG2 + /Nestin-GFP +), using a double-transgenic Nestin-GFP/NG2-DsRed mouse (Birbrair et al. 2013a, 2014a). The cerebral pericyte subsets differ in their functions, as i.e., after brain injury, only type-1 pericytes participate in the scar tissue formation (Birbrair et al. 2014a). What is the exact role of these pericyte subpopulations during glioma progression remains unknown. And, more interestingly, whether periostin overexpression is important in the function of each of these subtypes should be explored in future studies. Additionally, it is necessary to examine whether different pericytes' subtypes change their functions after being exposed to glioma cells. Moreover, the exact identity of glioma cancer cells is not well defined. These tumors are composed of heterogeneous subclones of cancer, including glioma stem cells. Whether these cancer cell subsets vary in their interactions with pericytes subpopulations should be addressed.

Importantly, the perivascular anatomical location is not exclusive of pericytes. Other cellular populations have been shown to be located in the same anatomical position: i.e., smooth muscle cells, fibroblasts (Soderblom et al. 2013), adventitial cells (Crisan et al. 2012), Lepr + cells (Sena et al. 2017a), Gli1 + cells (Sena et al. 2017b), and even macrophages (Bechmann et al. 2001; Guillemin and Brew 2004). Periostin was also identified in other cells, such as human gastric cancer-associated fibroblasts. By functional studies, the authors demonstrated that periostin stimulated human gastric cancer cell line OCUM-2MLN to proliferate via ERK pathway activation in vitro. Also, co-inoculation with mouse fibroblast NIH3T3 overexpressing periostin increases tumoral growth and invasiveness in vivo (Kikuchi et al. 2014). Interestingly, patients with high levels of periostin expression in cholangiocarcinoma-associated fibroblasts have poor prognosis compared to those with low levels (Utispan et al. 2010). One major distinction that outlines pericytes in comparison to other perivascular cells is that pericytes are covered by the perivascular basal lamina mainly composed of laminin (Allsopp and Gamble 1979; Payne et al. 2020). Huizer and colleagues used PDGFRβ to identify periostin expression in pericytes (Huizer et al. 2020). Nevertheless, PDGFRβ is a known marker of fibroblasts in the central nervous system (Soderblom et al. 2013; Spitzer et al. 2012). Although none of brain pericyte markers are specific, when used in combination they clearly distinguish pericytes from other cell types. Single pericyte RNA sequencing analysis will confirm the expression of important molecules in glioma pericytes in future works.

Huizer and colleagues performed the functional studies using cell lines derived from normal brain (Huizer et al. 2020). It would be interesting to analyze the behavior of pericytes derived from human glioma biopsies of different glioma grades. This would help to correlate pericytes behavior with glioma progression. Head and neck squamous cell carcinoma (HNSCC)-derived periostin promotes

lymphangiogenesis through the upregulation of VEGF-C in vitro. In HNSCC human samples, periostin can be detected in the cytoplasm of tumoral cells. Periostin expression had no correlation with the number of peri and intratumoral lymphatic vessels, but was significantly associated with lymphatic invasion in HNSCC human samples (Kudo et al. 2012). Furthermore, non-small cell lung cancer patients whose tumors showed low levels of periostin expression on mesenchymal cells had almost twice 3-year survival rate increased (81.5%) compared with those with high levels of periostin expression (45.4%) (Hong et al. 2013).

Periostin also have been used as a therapeutic target, its neutralization with a monoclonal antibody induced ovarian cancer cell apoptosis, reduced migration and inhibited invasion in vitro, as well as decreased ovarian cancer growth and metastasis in vivo (Zhu et al. 2011). Is important to notice that Huizer and collegues (Huizer et al. 2020) observed periostin expression mainly in grade I (pilocytic astrocytoma) and in grade IV (glioblastoma) astrocytomas. Grade II/III astrocytomas and grade II/III oligodendrogliomas expressed the same levels of periostin as normal brain tissue. Diagnostic markers in clinical practice are useful to differentiates gliomas, for example, distinguishing small cell glioblastomas from high-grade oligodendrogliomas, or high-grade astrocytomas that are likely to behave as aggressively as glioblastomas (Tanaka et al. 2013). Thus, the use of periostin as a diagnostic marker in gliomas deserves further investigation. An enormous challenge now is to translate basic research into clinic. Bettering the accessibility to human cancer tissue samples will be crucial to achieve this goal. Future studies will establish whether the periostin in glioma pericytes play critical role for tumor progression.

Multiple important functions of pericytes have been discovered in the last two decades. Pericytes interact with astrocytes to regulate the maintenance of the blood–brain barrier (Bell et al. 2010; Thanabalasundaram et al. 2011; Kamouchi et al. 2011). They also participate in vascular development, maturation and remodeling, as well as contributing to its normal architecture and permeability (Soriano 1994; Enge et al. 2002; Hellstrom et al. 2001; Leveen et al. 1994; Lindahl et al. 1997). Pericytes regulate the blood flow (Pallone et al. 2003), and recent studies showed that pericytes can function as stem cells, generating several other cell types, including neural cells (Birbrair et al. 2014b). Pericytes also play immune functions by regulating lymphocytes activation (Balabanov et al. 1999; Tu et al. 2011; Verbeek et al. 1995; Fabry et al. 1993), by attracting innate leukocytes that exit through the sprouting vessels (Stark et al. 2013), by contributing to the clearance of toxic cellular byproducts, as pericytes possess phagocytic activity (Caspani et al. 2014), and by affecting blood coagulation (Kim et al. 2006; Fisher 2009; Bouchard et al. 1997; Jeynes 1985; Balabanov et al. 1996; Thomas 1999; Hasan and Glees 1990; Castejon 2011). Importantly, within the glioma microenvironment, pericytes also have been shown to induce immunosuppression (Valdor et al. 2017; Sena et al. 2018). Whether periostin is essential for other pericyte functions in special within the tumor microenvironment remains to be elucidated.

Conclusion

In conclusion, the study by Huizer and colleagues suggest that periostin expressed by pericytes in the cerebral microenvironment during glioma progression plays a critical role in tumoral angiogenesis. However, our understanding of glioma microenvironment and the role of pericytes within it still remains limited, and the interactions of distinct glioma constituents during disease development should be elucidated in future studies.

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Compliance with Ethical Standards

Conflict of Interest The authors declare that they have no conflict of interest.

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